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Domiciliary use of transcutaneous electrical stimulation for patients with obstructive sleep apnoea: a conceptual framework for the TESLA home programme

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Abstract: Obstructive sleep apnoea (OSA) is a global health problem of increasing prevalence. Effective treatments are available with continuous positive airway pressure (CPAP) therapy and mandibular advancement devices (MAD). However, there is limited long-term adherence to therapy, as CPAP and MAD require permanent usage to avoid recurrence of the symptoms and adverse ill health. Alternative treatments would aid in the treatment cascade to manage OSA effectively whenever standard therapy has been trialled and failed. Hypoglossal nerve stimulation (HNS), an invasive approach to stimulate the pharyngeal dilator muscles of the upper airway during sleep, has been approved for the treatment of OSA by several healthcare systems in recent years. In parallel to the development of HNS, a non-invasive approach has been developed to deliver electrical stimulation. Transcutaneous electrical stimulation in obstructive sleep apnoea (TESLA) uses non-invasive electrical stimulation to increase neuromuscular tone of the upper airway dilator muscles of patients with OSA during sleep. Data from previous feasibility studies and randomised controlled trials have helped to identify a subgroup of patients who are “responders” to this treatment. However, further investigations are required to assess usability, functionality and task accomplishment of this novel treatment. Consideration of these factors in the study design of future clinical trials will strengthen research methodology and protocols, improve patient related outcome measures and assessments, to optimise this emerging therapeutical option. In this review, we will introduce a conceptual framework for the TESLA home programme highlighting qualitative aspects and outcomes.

Keywords: Hypoglossal nerve stimulation (HNS); neural stimulation; continuous positive airway pressure (CPAP); sleepiness; compliance

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Introduction

Obstructive sleep apnoea (OSA) is a global health problem associated with increased morbidity and mortality (1-4). Patients with OSA experience repetitive upper airway closure during sleep which results in complete or partial cessation of airflow and causes oxygen desaturations; the airway closure leads to arousal from sleep, causing sleep fragmentation and daytime symptoms (5). OSA puts patients and others at risk of injury due to road traffic accidents (6,7) caused by drowsiness and results in decreased neurocognitive function (8); OSA is associated with increased cardiovascular risk (3), hypertension (9,10) and endothelial dysfunction (11), potentially contributing to myocardial infarction (12), stroke (13) and congestive heart failure (14). In addition to hypertension, risk factors associated with OSA include the male gender, age, obesity and smoking (15-18).

Various factors contribute to upper airway obstruction during sleep (19,20), including an abnormal anatomy (e.g., a narrow upper airway, enlarged tonsils, adenoids, retrognathia, obesity) and decreased neuromuscular tone (5,21-24). Different anatomical levels of upper airway obstruction, the severity of OSA, posture and sleep state can all influence the efficacy of treatment (24-28). The best way to assess OSA severity is overnight polysomnography ("sleep study"), although symptom questionnaires and risk scores are used in the clinical setting and in population-based studies, and are essential to identify patients and define the syndrome (21,29).

Currently available treatments for OSA include continuous positive airway pressure (CPAP), mandibular advancement devices (MAD) and dental devices (30-33), lifestyle advice, weight loss and positional therapy (34), maxillo-mandibular surgery and ENT interventions (e.g., uvulopalatopharyngoplasty) (35) and, less frequently, non-invasive ventilation (5). CPAP remains the Gold-standard treatment (36,37), however, there is limited long-term adherence to CPAP and only about half of the patients will use it for the recommended four hours a night during at least five days a week after one year (5,38,39). The clear association between obesity and sleep apnoea (5,23,40-43) underlines the importance of developing effective treatments for weight loss to complement CPAP therapy.

Hypoglossal nerve stimulation (HNS) has been recently developed as a novel treatment for OSA (44,45). It requires the implantation of a stimulator cuff that is in contact with the hypoglossal nerve; it works by increasing the

neuromuscular tone of the upper airway dilator muscles and thereby maintaining a patent upper airway during sleep (46-48). However, delivery of electrical stimulation is not exclusively an invasive option. A similar effect on the neuromuscular tone of the upper airway dilator muscles (49,50) can be achieved non-invasively by the use of transcutaneous electrical stimulation (46,47). Patient-and-public-involvement (PPI) surveys have shown that patients with OSA, even those who are adherent to CPAP therapy, are interested in the development and the testing of novel and particularly non-invasive treatments (51). Participation in and recruitment to future clinical trials will benefit from this involvement.

In 2014, HNS was approved by the United States Food and Drug Administration (FDA) (52), and there are now post-market research registries and studies (e.g., Germany). In the UK, the National Institute for Health and Care Excellence (NICE) has published its interventional procedure guidance on HNS (IPG598) (53). The transcutaneous approach (TESLA) is currently undergoing a domiciliary feasibility study (TESLA home; NCT03160456, for the protocol see online: <http://fp.amegroups.cn/cms/jtd.2019.05.04-1.pdf>), involving three-months treatment and assessment. The TESLA home methodology delivers electrical current via transcutaneous patches in the submental area, targeting the genioglossus muscle to maintain airway patency. This randomised controlled trial recruits patients with OSA (apnoea-hypopnoea index 5-35/hour) who have failed to use CPAP effectively (usage <4 hours/night). Slim, overweight and mildly obese subjects (body-mass index, BMI <32 kg/m²) with an antero-posterior wall collapse and a slim neckline are known to represent the phenotype of "responders" to this therapy. In particular women with OSA have been identified to benefit from this method (50). Similar to the selection criteria utilised for HNS, morbidly obese subjects with more severe OSA, multi-level or concentric upper airway collapse do not seem to sufficiently benefit and are excluded from upper airway stimulation trials. In addition to objectively measuring the effectiveness of electrical stimulation on preventing upper airway collapse, qualitative assessments are important to test the feasibility of such a novel treatment. Patients' feedback will help to determine the feasibility of domiciliary transcutaneous electrical stimulation, design future clinical trials and inform further modification of the technology and the device (54). In this review, we will introduce a conceptual framework for the TESLA home programme to highlight qualitative aspects and outcomes.

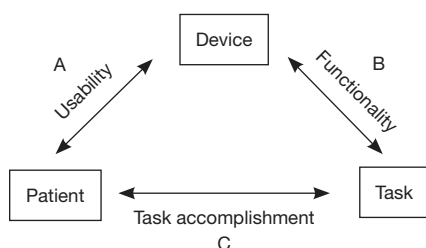


Figure 1 Schematic proposal of a conceptual framework TESLA. A: refers to “usability” to reflect the interaction between patient and device; B: refers to “functionality” to describe the link between device and task; C: refers to “task accomplishment” to assess the link between patient and task.

Conceptual framework

A framework was developed based on the conceptual idea to capture relevant aspects of the research undertaken in the TESLA programme, analyse and address health-regulatory body requirements (Medicines & Healthcare Products Regulatory Agency, MHRA) and produce qualitative data from clinical trials that are not directly linked to primary or secondary outcomes of the clinical trial (54). The published literature of electrical stimulation for sleep apnoea was screened and databases were searched (PubMed, Web of Science and Google Scholar) using specific criteria (“electrical stimulation”, “transcutaneous electrical stimulation”, “hypoglossal nerve stimulation”, “Obstructive Sleep Apnoea”, “treatment”, “usability”, “medical devices”, “MHRA”); the found results were assessed by two independent reviewers (R Tas, M Beach) and included for discussion with two other reviewers (M Nido, J Steier) to generate and refine a model of a conceptual framework for the TESLA programme. The described conceptual framework was created with the intention to better assess the interaction between the three domains “medical device” (TESLA), “user” (patient) and “task” (OSA treatment) (54) which are defined as (I) “usability”, (II) “functionality” and (III) “task accomplishment” (Figure 1).

“Usability”

The “usability” describes the degree to which the patient can make use of a medical device, to achieve quantifiable objectives efficiently, effectively and satisfactorily (55) (Figure 1). The user experience is complex and can, in part, be explained by a model that incorporates seven aspects of a treatment from the perspective of the user: whether it is

usable, valuable, useful, desirable, accessible, credible and findable (56). “Usability” testing is considered a cornerstone in user-centred design, as it provides information about the machine-user interaction (57).

The perceived “usability” of a treatment can affect adherence, which is the limiting factor for other sleep apnoea treatments like CPAP therapy and MAD. It is essential to understand this feature to better treat non-adherent patients. Long-term adherence depends on how individuals judge their personal need for a treatment relative to their concerns about its potential adverse effects. Adherence is a primary determinant of the effectiveness of treatment, good long-term adherence improves the effectiveness of therapeutic interventions (58).

To assess usability quantitative and qualitative approaches and methods can be used (59). Questionnaires (quantitative method) can rate the “ease of use”, “instructions for use”, and the “clarity of the design”, as well as ergonomics on given rating scales. With qualitative methods, such as (semi-)structured interviews, additional information can be gathered assessing patients’ “adherence to intended use”, or obvious design errors. The collected quantitative and qualitative data can then be used to address issues of “usability” and improve the machine-user interaction. Patients’ diaries to record practicability and potential adverse events can further measure “usability” of transcutaneous electrical stimulation for OSA (60).

Psychological and personal aspects of a patient are essential characteristic when discussing “usability”, as they will affect any interaction with medical devices (61-63). Additionally, the attitude to treatment can be positive, negative or neutral based on previous experiences and expectations, as it is set out in motivational theories, such as the Valence-Instrumentality-Expectancy (V-I-E) model (64). Motivation to use a device can therefore be explained as a multiplied connection of expectancy of a certain outcome (“the device will help to improve my health”) and the value of the result (“better health is of high relevance to the patient”).

The following assessment can assist to address usability of the method:

- ❖ Patient comfort and device acceptance: Semiquantitative visual analogue scales can be used to assess the comfort of a new treatment (‘very much/very good’/“0” points, to ‘not at all/terrible’/“10”points) (54). In the context of TESLA, this can be used to identify adverse effects that can arise from the treatment, such as ‘skin discomfort’.



Figure 2 Picture of one of the prototypes of the TESLA programme attached to the submental area.

- ❖ Qualitative and descriptive parameters and feedback: Patient feedback about usage, acceptance, problems and perceived benefits, may assess acceptability of a novel treatment. Difficulties with the device, such as reliability, faults, ease of use, can be useful to modify the feasibility of the machine and, in the case of the TESLA programme, also the skin interface (hydrogel/patches).

In the context of TESLA-home the described features play an important role (*Figure 2*; online: <http://fp.amegroups.cn/cms/jtd.2019.05.04-1.pdf>) and patient-and-public-involvement (PPI) (51) was undertaken at an early stage to understand the user, the task and physiological requirements, encourage early and active involvement, incorporate user-centred evaluations, address the entire user experience, encourage a multi-disciplinary design, and continuously engage with the users during the process (ISO 9241-210) (65).

“Functionality”

The “functionality” tests the interaction between the ‘device’ and the ‘task’, it could also be described as efficacy in achieving a sufficient contraction of the dilator muscles of the upper airway to avoid upper airway obstruction (*Figure 1*). It assesses whether the muscles are sufficiently stimulated, and is further characterised by the suitability of the method, accuracy, interoperability, security, and functionality compliance; these features aim to satisfy the stated or implied needs (66). To maximise the effect and increase the neuromuscular tone of the genioglossus, improve upper airway patency and, thereby, treat OSA, some parameters including several basic properties of the medical device such as current, pulse width, stimulation

frequency, wave form and pad shapes (size, location, uni- vs. bilateral stimulation, material), and stimulation timing (triggered, intermittent, continuous) could be varied to further refine the treatment. These variables impact on the generated force, the fatiguability on the neuromuscular junction, the skin sensation and the tolerability of the method.

Relevant MHRA guidelines (67)

The MHRA have issued relevant guidance on device resilience. To be resilient, the medical device’s functioning and performance should not be affected adversely through normal conditions of use over time. Furthermore, the device measurements and outputs must be accurate and remain so for the duration of the devices use with any accuracy limits clearly specified. Any measurements made should be expressed in the appropriate units as described in the Council Directive 80/181/EEC, and functions involving measuring and monitoring should be developed according to ergonomic principles. Devices involving electronic systems must be designed to function according to their intended use with ensured reliability and repeatability of performance.

Specific to the TESLA methodology, it is important to measure a number of quantitative variables that help the understanding of the effect on the targeted muscles, describe physiological changes on the airway structure and the skin sensation of the electrical activity:

- ❖ Imaging to observe muscle contraction and improvement in upper airway patency:
 - ♦ Upper airway magnetic resonance imaging (MRI) or computer tomography (CT) can be used to accurately visualize and calculate the diameter (mm^2) of the upper airway awake and during sleep, as well as with the stimulation turned ‘on’ or ‘off’.
 - ♦ Ultrasound is ubiquitous available in hospitals and can be used to identify and localise upper airway obstruction (68). The genioglossus can be visualised in different planes (49,68) and the contraction of this muscle during stimulation can be tested at the bedside. Ultrasound measurements (frequency 5 to 13 MHz, *Figure 3*) can track significant contraction in the genioglossus during stimulation.
 - ♦ Endoscopy of the upper airway is an option to evaluate the severity of upper airway obstruction (69,70) and offers the chance to assess upper airway patency during stimulation (*Figure 4*).

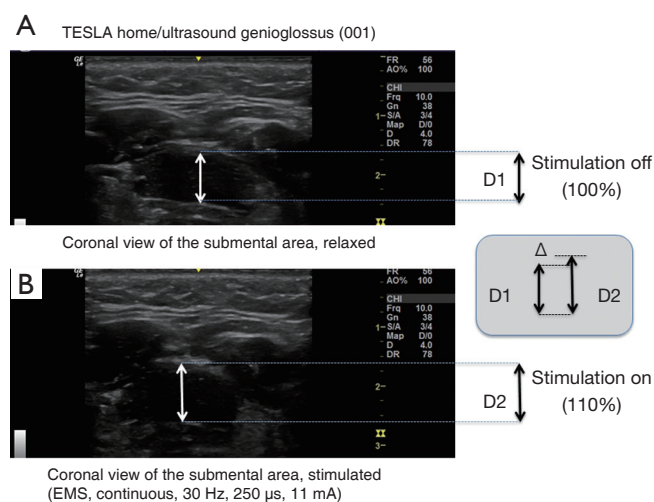


Figure 3 Ultrasound images of the genioglossus muscle, (A) it shows the relaxed muscle (without stimulation) in a coronal view, (B) it shows the muscle during electrical stimulation and the resulting change in the diameter caused by contraction. As the muscle contracts, it shortens, pulling the pharyngeal wall towards the anterior direction. An increase in the radius by +10% results in an approximate increase in the cross-sectional area (CSA) of the muscle of +21%, assuming a round model ($CSA = \pi \times r^2$).

❖ Electromyography of the submental muscles can record targeted muscle activity (49,71-73).

For the TESLA home trial, physiological measurements focus on upper airway morphology and muscle contractions during electrical stimulation using ultrasound, upper airway endoscopy in the awake participants and functional assessments (see online: <http://fp.amegroups.cn/cms/jtd.2019.05.04-1.pdf>); these measurements are available at the bedside in most clinical settings.

“Task accomplishment”

The interaction between the user and the task/goal can be further described to determine “task accomplishment”, which can be assessed subjectively as well as objectively. Patients’ preconception of what they believe resembles a successful treatment compared with the treating teams’ point of view may not be entirely compatible, as they can prioritise different criteria [e.g., sleepiness *vs.* apnoea-hypopnoea index (AHI)].

Objectively, treatment data can be measured using tools that provide quantitative results related to the assessment of sleep, restoration of sleep architecture and improved

symptom control, quality of life and mastery. The main outcome parameter for clinical trials in OSA is typically the AHI that is used to define severity of the disease. However, the following parameters can be used to further address objective assessments:

❖ Nocturnal polysomnography results are the Gold standard to assess OSA severity and treatment efficacy (74). Certain indices derived from the polysomnography are of importance when describing upper airway patency and functional assessment during sleep:

- ♦ Apnoea-hypopnoea index (AHI): the AHI is the number of apnoeas (airflow absence for ≥ 10 seconds) and hypopnoeas (reduction in respiratory effort by $\geq 30\%$, associated with oxygen desaturation of $\geq 3\%$ and/or arousal) per hour of recorded sleep. Excessive daytime sleepiness and an AHI greater than 5 are key features of OSA. The AHI is a standardised method that evaluates both severity and treatment outcome for OSA (mild OSA: AHI 5–14/hour, moderate OSA: AHI 15–30/hour, and severe OSA: AHI >30 /hour) (75). The AHI does not assess the time spent in respiratory events or allow the differentiation of hypopnoeas or apnoeas (76). An incomplete reopening of the upper airway using an insufficient treatment may convert apnoeas into hypopnoeas, which would not be reflected accurately in the AHI. However, the AHI is a widely accepted tool for assessing OSA (52).
- ♦ Oxygen Desaturation Index (ODI): the ODI can be recorded according to the desaturation threshold, most commonly the 3% or the 4% ODI are reported. The ODI is used to assess OSA in clinical settings and when tracking treatment of OSA (77-81).
- ♦ Sleep Architecture: this term refers to the cyclical pattern of sleep cycles and the preserved features of a hypnogram, including non-rapid eye movement (N1-3) and rapid eye movement (REM) sleep. OSA causes disruption of the natural sleep architecture, with frequent arousals leading to numerous sleep stage shifts and abnormal cycling of sleep (82). On CPAP therapy, patients with OSA have an improved sleep quality (83). Similarly, the recording of the hypnogram can supplement the assessment of treatment and “task accomplishment”.
- ♦ Arousal Index (AI): the AI is defined as the number of awakenings per hour during a recorded sleep study period, it is used in parallel to the hypnogram to

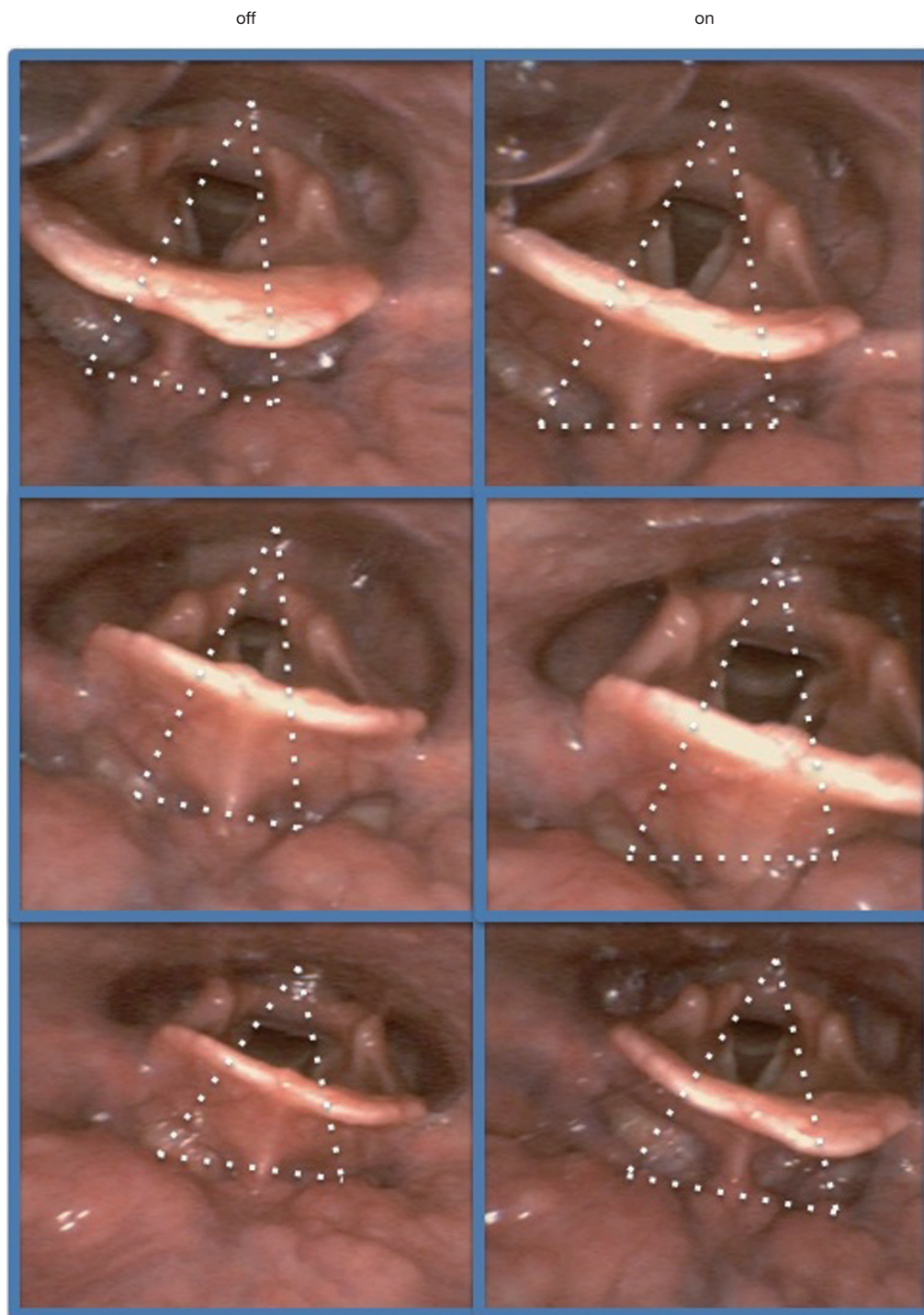


Figure 4 Endoscopic images of the upper airway. The left panels show the upper airway with the vocal cords and the epiglottis while electrical stimulation is turned “off”, the right panel shows the same area when stimulation is turned “on”. The anterior-posterior diameter increases with stimulation, the tonsilla lingualis becomes visible just underneath the epiglottis when electrical stimulation is turned on (right lower panel).

understand sleep fragmentation and architecture (84).

- ♦ Snoring: snoring is a symptom associated with OSA that predominantly affects partners and others. However, the percentage of the night that patients snore may not reflect the severity of OSA (85), although there is a positive correlation between louder snoring and severe OSA (86).

In addition, subjective assessments of “task accomplishment” are important, as patients need to be offered the opportunity to report on usage, sensation, expectation and efficacy of the treatment. The following tools may provide guidance for these assessments:

- ❖ Epworth Sleepiness Scale (ESS): this is a commonly used questionnaire including eight questions about patient’s perception of sleepiness, scoring from “0” (not at all) to “3” (highly likely to doze). The minimal total score is “0” and the maximum “24” points (87). A score higher than 8 points has a 76% specificity for OSA (88) and treatments for OSA are considered effective if the ESS score improves. Accuracy can be improved through the use of a patient-partner consensus score (89,90); pictorial (91) and online ESS (92) are used for screening. However, the ESS remains a subjective report and is subject to relevant sources of bias and inaccuracy (93). Despite its limitations, the minimal clinically important difference (MCID) for the ESS has been described as an improvement of more than two points (94).
- ❖ Berlin Questionnaire (BQ): this questionnaire is typically used to screen for OSA. The BQ includes questions about snoring, daytime somnolence, body mass index (BMI), and hypertension (95). It is a brief and validated screening tool that identifies people in the community who are at risk of OSA (96). It has a high sensitivity but low specificity (97,98).
- ❖ Stanford Sleepiness Scale (SSS): the SSS is a self-reported questionnaire to assess how awake the patient feels throughout the day (99). It can be used to compare sleepiness in hourly intervals of the day, for example prior to new treatment and to assess success thereafter. The SSS can be a useful measure to observe individual progress and to compare results with other studies (99).
- ❖ Hospital Anxiety and Depression Scale (HADS): the HADS is a tool used for assessing anxiety and depression (100,101). It is widely used in clinical practice and research. It contains fourteen straightforward questions (102). The link between

depression/anxiety and chronic conditions like OSA is well reported (103). Hence, this tool is important in the assessment of how OSA affects the mental health of an individual. In addition, mental health disorders often co-exist with OSA. These conditions can include depression, anxiety, schizophrenia, bipolar disorder, post-traumatic stress disorder (PTSD) and substance use disorders (104). Used as a screening tool, the HADS can be added prior to commencing on new treatments, and repeatedly measured to follow up on the treatment effect (67).

- ❖ Functional Outcomes of Sleep Questionnaire (FOSQ): this is a validated questionnaire to assess the impact of sleepiness on a patient’s ability to perform activities of daily living (ADLs) (105). The questionnaire contains 30 questions, covering 5 subscales (General Productivity, Social Outcome, Activity Level, Vigilance, Intimate Relationships and Sexual Activity) (106).
- ❖ European Quality of Life five dimensions scale (EQ-5D): the EQ-5D is used for the standardised measurement of health outcomes (107,108) and is available in 130 languages (109); the results can be used for reference-case analyses and for health-economics (110).
- ❖ Other Questionnaires: according to a systematic review of outcome measures for OSA, the most suitable additional assessments include the Maugeri OSA syndrome (MOSAS) questionnaire (quality of life), the sleep apnoea quality of life index (SAQLI), the OSA patient-orientated severity index (OSAPOS) and the Quebec sleep questionnaire (QSQ) (100,111).

The discussion about suitable outcome parameters in OSA remains contentious, partially due to the conflict of subjective *vs.* objective disease burden (subjective symptoms *vs.* objective disease severity). However, for any clinical trial it is important to capture enough data to describe the ‘syndrome’ (symptoms and sleep apnoea pathophysiology) and, thus, the TESLA home trial includes all of the above objective markers, including full polysomnography, and many of the symptom questionnaires plus some semi-quantitative interviews during the follow up period (see online: <http://fp.amegroups.cn/cms/jtd.2019.05.04-1.pdf>).

Conclusions

In order to assess a novel treatment method, as used in the TESLA home trial, it is important to understand additional components other than the primary outcome parameters of

change in disease severity in response to treatment; these features define treatment uptake by addressing “usability”, “functionality” and “task accomplishment”. The conceptual framework for future studies using TESLA methodology acknowledges these key elements to address relevant guidelines, including those required by the NICE and the MHRA.

The TESLA home programme incorporates the following points:

- ❖ Development of a human factors engineering (HFE) programme within the existing product development process that satisfies regulations and standards.
- ❖ Design of user interfaces that not only enable safe and effective user interactions, but are also perceived as usable and appealing by early and continuous involvement of the user (PPI).
- ❖ Suitable labels and information for users that enable and enhance the user's ability to engage with the product effectively and safely (112) and disseminate information from clinical trials and device performance.

The proposed patient related outcome measures (PROMS) have been designed for future studies and could be used to test the efficacy of the treatment; accurate recording of PROMS will provide invaluable information from clinical trials to refine the method, optimise future treatment performance and design study protocols.

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Footnote

Conflicts of Interest: J Steier is named inventor on patent WO 2016/124739 A1 ('Apparatus for treatment of snoring and sleep apnoea') on behalf of King's College London and Guy's & St Thomas' NHS Foundation Trust. Other authors have no conflicts of interest to declare.

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